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=> index bioscience chemistry patents meetings
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       BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
       CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
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=> s xrcc4 and ku and (DNA (w) ligase (w) IV)
         18   FILE BIOSIS
          2   FILE BIOTECHABS
          2   FILE BIOTECHDS
         10   FILE BIOTECHNO
          1   FILE CABA
         12   FILE CANCERLIT
         19   FILE CAPLUS
  15 FILES SEARCHED...
          5   FILE DGENE
  29 FILES SEARCHED...
          1   FILE EMBAL
         10   FILE EMBASE
         12   FILE ESBIOBASE
          1   FILE FEDRIP
         14   FILE LIFESCI
         25   FILE MEDLINE
          1   FILE NTIS
  49 FILES SEARCHED...
          2   FILE PASCAL
         19   FILE SCISEARCH
          7   FILE TOXCENTER
          4   FILE USPATFULL
          2   FILE WPIDS
          2   FILE WPINDEX
  71 FILES SEARCHED...
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  98 FILES SEARCHED...
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L1   QUE XRCC4 AND KU AND (DNA (W) LIGASE (W) IV)

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L2 25 FILE MEDLINE
L3 19 FILE CAPLUS
L4 19 FILE SCISEARCH
L5 18 FILE BIOSIS
L6 14 FILE LIFESCI
L7 12 FILE CANCERLIT
L8 12 FILE ESBIOBASE
L9 10 FILE BIOTECHNO
L10 10 FILE EMBASE
L11 7 FILE TOXCENTER
L12 5 FILE DGENE
L13 4 FILE USPATFULL
L14 3 FILE PCTFULL
L15 2 FILE BIOTECHDS
L16 2 FILE PASCAL
L17 2 FILE WPIDS
L18 1 FILE CABA
L19 1 FILE EMBAL
L20 1 FILE FEDRIP
L21 1 FILE NTIS
L22 1 FILE DPCI
L23 1 FILE PATOSEP
L24 1 FILE PATOSWO

TOTAL FOR ALL FILES
L25 171 L1

=> s l25 and binding and (DNA (w) PK)
L26 10 FILE MEDLINE
L27 4 FILE CAPLUS
L28 3 FILE SCISEARCH
L29 3 FILE BIOSIS
L30 2 FILE LIFESCI
L31 5 FILE CANCERLIT
L32 2 FILE ESBIOBASE
L33 3 FILE BIOTECHNO
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L35 2 FILE TOXCENTER
L36 0 FILE DGENE
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L46 0 FILE DPCI
L47 0 FILE PATOSEP
L48 0 FILE PATOSWO

TOTAL FOR ALL FILES
L49 45 L25 AND BINDING AND (DNA (W) PK)

=> d l49 1-45 ibib abs

L49 ANSWER 1 OF 45 MEDLINE

ACCESSION NUMBER: 2002473447 IN-PROCESS
DOCUMENT NUMBER: 22220783 PubMed ID: 12235392
TITLE: **DNA-PK**-dependent **binding** of DNA ends to plasmids containing nuclear matrix attachment region DNA sequences: evidence for assembly of a repair complex.
AUTHOR: Mauldin Stanley K; Getts Robert C; Liu Wenjing; Stamato Thomas D
CORPORATE SOURCE: Lankenau Institute for Medical Research, 100 Lancaster Avenue, Wynnewood, PA 19096, USA and Genisphere, Incorporated, 4170 City Avenue, Philadelphia, PA 19131-1694, USA.
SOURCE: NUCLEIC ACIDS RESEARCH, (2002 Sep 15) 30 (18) 4075-87. Journal code: 0411011. ISSN: 1362-4962.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020918
Last Updated on STN: 20020918

AB We find that nuclear protein extracts from mammalian cells contain an activity that allows DNA ends to associate with circular pUC18 plasmid DNA. This activity requires the catalytic subunit of **DNA-PK** (DNA-PKcs) and **Ku** since it was not observed in mutants lacking **Ku** or DNA-PKcs but was observed when purified **Ku**/DNA-PKcs was added to these mutant extracts. Purified **Ku**/DNA-PKcs alone did not produce association of DNA ends with plasmid DNA suggesting that additional factors in the nuclear extract are necessary for this activity. Competition experiments between pUC18 and pUC18 plasmids containing various nuclear matrix attachment region (MAR) sequences suggest that DNA ends preferentially associate with plasmids containing MAR DNA sequences. At a 1:5 mass ratio of MAR to pUC18, approximately equal amounts of DNA end **binding** to the two plasmids were observed, while at a 1:1 ratio no pUC18 end **binding** was observed. Calculation of relative **binding** activities indicates that DNA end-**binding** activities to MAR sequences was 7-21-fold higher than pUC18. Western analysis of proteins bound to pUC18 and MAR plasmids indicates that **XRCC4, DNA ligase IV** and scaffold attachment factor A preferentially associate with the MAR plasmid in the absence or presence of DNA ends. In contrast, **Ku** and DNA-PKcs were found on the MAR plasmid only in the presence of DNA ends suggesting that **binding** of these proteins to DNA ends is necessary for their association with MAR DNA. The ability of DNA-PKcs/**Ku** to direct DNA ends to MAR and pUC18 plasmid DNA is a new activity for **DNA-PK** and may be important for its function in double-strand break repair. A model for DNA repair based on these observations is presented.

L49 ANSWER 2 OF 45 MEDLINE
ACCESSION NUMBER: 2002216939 MEDLINE
DOCUMENT NUMBER: 21950349 PubMed ID: 11953323
TITLE: Specific interaction of IP6 with human Ku70/80, the DNA-**binding** subunit of **DNA-PK**.
AUTHOR: Hanakahi Les A; West Stephen C
CORPORATE SOURCE: Cancer Research UK, London Research Institute, Clare Hall Laboratories, South Mimms, Hertfordshire EN6 3LD, UK.
SOURCE: EMBO JOURNAL, (2002 Apr 15) 21 (8) 2038-44. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020416
Last Updated on STN: 20020611

Entered Medline: 20020606

AB In eukaryotic cells, DNA double-strand breaks can be repaired by non-homologous end-joining, a process dependent upon Ku70/80, **XRCC4** and **DNA ligase IV**. In mammals, this process also requires **DNA-PK**(cs), the catalytic subunit of the DNA-dependent protein kinase **DNA-PK**. Previously, inositol hexakisphosphate (IP6) was shown to be bound by **DNA-PK** and to stimulate **DNA-PK** -dependent end-joining in vitro. Here, we localize IP6 **binding** to the Ku70/80 subunits of **DNA- PK**, and show that **DNA-PK**(cs) alone exhibits no detectable affinity for IP6. Moreover, proteolysis mapping of Ku70/80 in the presence and absence of IP6 indicates that **binding** alters the conformation of the Ku70/80 heterodimer. The yeast homologue of Ku70/80, yKu70/80, fails to bind IP6, indicating that the function of IP6 in non-homologous end-joining, like that of **DNA-PK**(cs), is unique to the mammalian end-joining process.

L49 ANSWER 3 OF 45 MEDLINE
ACCESSION NUMBER: 2001236211 MEDLINE
DOCUMENT NUMBER: 21153783 PubMed ID: 11124945
TITLE: Deficient DNA end joining activity in extracts from fanconi anemia fibroblasts.
AUTHOR: Lundberg R; Mavinakere M; Campbell C
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota Medical School, Minneapolis, Minnesota 55455, USA.
CONTRACT NUMBER: AG16678 (NIA)
CA61906 (NCI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Mar 23) 276 (12) 9543-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20020420
Entered Medline: 20010503

AB Fanconi anemia (FA) is a genetic disorder associated with genomic instability and cancer predisposition. Cultured cells from FA patients display a high level of spontaneous chromosome breaks and an increased frequency of intragenic deletions, suggesting that FA cells may have deficiencies in properly processing DNA double strand breaks. In this study, an in vitro plasmid DNA end joining assay was used to characterize the end joining capabilities of nuclear extracts from diploid FA fibroblasts from complementation groups A, C, and D. The Fanconi anemia extracts had 3-9-fold less DNA end joining activity and rejoined substrates with significantly less fidelity than normal extracts. Wild-type end joining activity could be reconstituted by mixing FA-D extracts with FA-A or FA-C extracts, while mixing FA-A and FA-C extracts had no effect on end joining activity. Protein expression levels of the DNA-dependent protein kinase (**DNA-PK**)/**Ku** -dependent nonhomologous DNA end-joining proteins **Xrcc4**, **DNA ligase IV**, Ku70, and Ku86 in FA and normal extracts were indistinguishable, as were DNA-dependent protein kinase and DNA end **binding** activities. The end joining activity as measured by the assay was not sensitive to the **DNA-PK** inhibitor wortmannin or dependent on the nonhomologous DNA end-joining factor **Xrcc4**. However, when DNA/protein ratios were lowered, the end joining activity became wortmannin-sensitive and no difference in end joining activity was observed between normal and FA extracts. Taken together, these results suggest that the FA fibroblast extracts have a deficiency in a DNA end joining process that is distinct from the **DNA-PK/Ku**-dependent nonhomologous DNA end

joining pathway.

L49 ANSWER 4 OF 45 MEDLINE
ACCESSION NUMBER: 2001202768 MEDLINE
DOCUMENT NUMBER: 21145441 PubMed ID: 11226171
TITLE: Novel functional requirements for non-homologous DNA end joining in Schizosaccharomyces pombe.
AUTHOR: Manolis K G; Nimmo E R; Hartsuiker E; Carr A M; Jeggo P A; Allshire R C
CORPORATE SOURCE: MRC Cell Mutation Unit, University of Sussex, Falmer, Sussex BN1, UK.
SOURCE: EMBO JOURNAL, (2001 Jan 15) 20 (1-2) 210-21.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412

AB DNA double strand break (DSB) repair by non-homologous end joining (NHEJ) in mammalian cells requires the Ku70-Ku80 heterodimer, the **DNA-PK** catalytic subunit DNA-PKcs, as well as **DNA ligase IV** and **Xrcc4**. NHEJ of plasmid DSBs in Saccharomyces cerevisiae requires **Ku**, **Xrcc4** and **DNA ligase IV**, as well as Mre11, Rad50, Xrs2 and DNA damage checkpoint proteins. Saccharomyces cerevisiae **Ku** is also required for telomere length maintenance and transcriptional silencing. We have characterized NHEJ in Schizosaccharomyces pombe using an extrachromosomal assay and find that, as anticipated, it is Ku70 and **DNA ligase IV** dependent. Unexpectedly, we find that Rad32, Rad50 (the S.pombe homologues of Mre11 and Rad50, respectively) and checkpoint proteins are not required for NHEJ. Furthermore, although S.pombe Ku70 is required for maintenance of telomere length, it is dispensable for transcriptional silencing at telomeres and is located throughout the nucleus rather than concentrated at the telomeres. Together, these results provide insight into the mechanism of NHEJ and contrast significantly with recent studies in S.cerevisiae.

L49 ANSWER 5 OF 45 MEDLINE
ACCESSION NUMBER: 2000458572 MEDLINE
DOCUMENT NUMBER: 20408964 PubMed ID: 10854421
TITLE: Interactions of the **DNA ligase IV-XRCC4** complex with DNA ends and the DNA-dependent protein kinase.
AUTHOR: Chen L; Trujillo K; Sung P; Tomkinson A E
CORPORATE SOURCE: Department of Molecular Medicine, Institute of Biotechnology, University of Texas Health Science Center, San Antonio, Texas 78245, USA.
CONTRACT NUMBER: ES07061 (NIEHS)
GM47251 (NIGMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Aug 25) 275 (34) 26196-205.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20020420
Entered Medline: 20000925

AB The DNA-dependent protein kinase (**DNA-PK**), consisting of **Ku** and the **DNA-PK** catalytic subunit

(DNA-PKcs), and the **DNA ligase IV-XRCC4** complex function together in the repair of DNA double-strand breaks by non-homologous end joining. These protein complexes are also required for the completion of V(D)J recombination events in immune cells. Here we demonstrate that the **DNA ligase IV-XRCC4** complex binds specifically to the ends of duplex DNA molecules and can act as a bridging factor, linking together duplex DNA molecules with complementary but non-ligatable ends. Although the DNA end-**binding** protein **Ku** inhibited DNA joining by **DNA ligase IV-XRCC4**, it did not prevent this complex from **binding** to DNA. Instead, **DNA ligase IV-XRCC4** and **Ku** bound simultaneously to the ends of duplex DNA molecules. **DNA ligase IV-XRCC4** and DNA-PKcs also formed complexes at the ends of DNA molecules, but DNA-PKcs did not inhibit ligation. Interestingly, DNA-PKcs stimulated intermolecular ligation by **DNA ligase IV-XRCC4**. In the presence of **DNA-PK**, the majority of the joining events catalyzed by **DNA ligase IV-XRCC4** were intermolecular because **Ku** inhibited intramolecular ligation, but DNA-PKcs still stimulated intramolecular ligation. We suggest that DNA-PKcs-containing complexes formed at DNA ends enhance the association of DNA ends via protein-protein interactions, thereby stimulating intermolecular ligation.

L49 ANSWER 6 OF 45 MEDLINE
ACCESSION NUMBER: 1999415934 MEDLINE
DOCUMENT NUMBER: 99415934 PubMed ID: 10485901
TITLE: Deletion of Ku86 causes early onset of senescence in mice.
AUTHOR: Vogel H; Lim D S; Karsenty G; Finegold M; Hasty P
CORPORATE SOURCE: Department of Pathology, Baylor College of Medicine, Houston, TX 77030, USA.
CONTRACT NUMBER: 1RO1CA76317-01 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Sep 14) 96 (19) 10770-5. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991014

AB DNA double-strand breaks formed during the assembly of antigen receptors or after exposure to ionizing radiation are repaired by proteins important for nonhomologous end joining that include Ku86, Ku70, **DNA-PK**(CS), **Xrcc4**, and **DNA ligase IV**. Here we show that ku86-mutant mice, compared with control littermates, prematurely exhibited age-specific changes characteristic of senescence that include osteopenia, atrophic skin, hepatocellular degeneration, hepatocellular inclusions, hepatic hyperplastic foci, and age-specific mortality. Cancer and likely sepsis (indicated by reactive immune responses) partly contributed to age-specific mortality for both cohorts, and both conditions occurred earlier in ku86(-/-) mice. These data indicate that Ku86-dependent chromosomal metabolism is important for determining the onset of age-specific changes characteristic of senescence in mice.

L49 ANSWER 7 OF 45 MEDLINE
ACCESSION NUMBER: 1999238412 MEDLINE
DOCUMENT NUMBER: 99238412 PubMed ID: 10219089
TITLE: Isolation of Ku70-**binding** proteins (KUBs).
AUTHOR: Yang C R; Yeh S; Leskov K; Odegaard E; Hsu H L; Chang C; Kinsella T J; Chen D J; Boothman D A

CORPORATE SOURCE: Department of Radiation Oncology and Department of Pharmacology and the Ireland Cancer Center,Laboratory of Molecular Stress Responses, Case Western Reserve University, BRB-326 East,10900 Euclid Avenue, Cleveland, OH 44106-4942, USA.
CONTRACT NUMBER: CA-50595 (NCI)
CA-ES78530 (NCI)
CA50519 (NCI)
SOURCE: NUCLEIC ACIDS RESEARCH, (1999 May 15) 27 (10) 2165-74.
Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990712
Last Updated on STN: 20020420
Entered Medline: 19990624

AB DNA-dependent protein kinase (**DNA-PK**) plays a critical role in resealing DNA double-stand breaks by non-homologous end joining. Aside from **DNA-PK**, **XRCC4** and **DNA ligase IV**, other proteins which play a role(s) in this repair pathway remain unknown; **DNA-PK** contains a catalytic subunit (DNA-PKcs) and a DNA **binding** subunit (Ku70 and Ku80). We isolated Ku70-**binding** proteins (KUB1-KUB4) using yeast two-hybrid analyses. Sequence analyses revealed KUB1 to be apolipoprotein J (apoJ), also known as X-ray-inducible transcript 8 (XIP8), testosterone-repressed prostate message-2 (TRPM-2) and clusterin. KUB2 is Ku80. KUB3 and KUB4 are unknown, >10 kb trans-cripts. Interactions of apoJ/XIP8 or KUB3 with Ku70 were confirmed by co-immunoprecipitation analyses in MCF-7:WS8 breast cancer or IMR-90 normal lung fibroblast cells, respectively. The interaction of apoJ/XIP8 with Ku70 was confirmed by far-western analyses. Stable over-expression of full-length apoJ/XIP8 in MCF-7:WS8 caused decreased Ku70/Ku80 DNA end **binding** that was restored by apoJ/XIP8 monoclonal antibodies. The role of apoJ/XIP8 in ionizing radiation resistance/sensitivity is under investigation.

L49 ANSWER 8 OF 45 MEDLINE
ACCESSION NUMBER: 1999045638 MEDLINE
DOCUMENT NUMBER: 99045638 PubMed ID: 9826654
TITLE: DNA end-joining catalyzed by human cell-free extracts.
AUTHOR: Baumann P; West S C
CORPORATE SOURCE: Imperial Cancer Research Fund, Clare Hall Laboratories, South Mimms, Herts EN6 3LD, United Kingdom.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Nov 24) 95 (24) 14066-70.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20020420
Entered Medline: 19981228

AB Mammalian cells defective in DNA end-joining are highly sensitive to ionizing radiation and are immunodeficient because of a failure to complete V(D)J recombination. By using cell-free extracts prepared from human lymphoblastoid cell lines, an in vitro system for end-joining has been developed. Intermolecular ligation was found to be accurate and to depend on **DNA ligase IV/Xrcc4** and requires Ku70, Ku86, and DNA-PKcs, the three subunits of the DNA-activated protein kinase **DNA-PK**. Because these activities are involved in the cellular resistance to x-irradiation and V(D)J recombination, the development of this in vitro system provides an

important advance in the study of the mechanism of DNA end-joining in human cells.

L49 ANSWER 9 OF 45 MEDLINE
ACCESSION NUMBER: 1998342672 MEDLINE
DOCUMENT NUMBER: 98342672 PubMed ID: 9677708
TITLE: DNA breakage and repair.
AUTHOR: Jeggo P A
CORPORATE SOURCE: MRC Cell Mutation Unit, University of Sussex, Brighton, United Kingdom.
SOURCE: ADVANCES IN GENETICS, (1998) 38 185-218. Ref: 152
Journal code: 0370421. ISSN: 0065-2660.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980820
Last Updated on STN: 20020420
Entered Medline: 19980807

AB For many years it has been evident that mammalian cells differ dramatically from yeast and rejoin the majority of their DNA DSBs by a nonhomologous mechanism, recently termed NHEJ. In the last few years a number of genes and proteins have been identified that operate in the pathway providing insights into the mechanism. These proteins include the three components of **DNA-PK**, **DNA ligase IV**, and **XRCC4**. In yeast Sir2, -3, and -4 proteins are also involved in the process and therefore are likely to play a role in higher organisms. Studies with yeast suggest that NHEJ is an error-free mechanism. Although the process is far from understood, it is likely that the **DNA-PK** complex or **Ku** alone acts in a complex with the Sir proteins possibly protecting the ends and preventing random rejoining. Further work is required to establish the details of this mechanism and to determine whether this represents an accurate rejoining process for a complex break induced by ionizing radiation. It will be intriguing to discover how the cell achieves efficient and accurate rejoining without the use of homology. Interactions between the components of **DNA-PK** and other proteins playing a central role in damage response mechanisms are beginning to emerge. Interestingly, there is evidence that DNA repair and damage response mechanisms overlap in lower organisms. The overlapping defects of the yeast **Ku** mutants, tell mutants, and AT cell lines in telomere maintenance further suggest overlapping functions or interacting mechanisms. A challenge for the future will be to establish how these different damage response mechanisms overlap and interact.

L49 ANSWER 10 OF 45 MEDLINE
ACCESSION NUMBER: 1998262931 MEDLINE
DOCUMENT NUMBER: 98262931 PubMed ID: 9600082
TITLE: Non-histone chromosomal proteins HMG1 and 2 enhance ligation reaction of DNA double-strand breaks.
AUTHOR: Nagaki S; Yamamoto M; Yumoto Y; Shirakawa H; Yoshida M; Teraoka H
CORPORATE SOURCE: Department of Pathological Biochemistry, Tokyo Medical and Dental University, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 May 8) 246 (1) 137-41.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806

ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 20020420
Entered Medline: 19980616

AB **DNA ligase IV** in a complex with **XRCC4** is responsible for DNA end-joining in repair of DNA double-strand breaks (DSB) and V(D)J recombination. We found that non-histone chromosomal high mobility group (HMG) proteins 1 and 2 enhanced the ligation of linearized pUC119 DNA with **DNA ligase IV** from rat liver nuclear extract. Intra-molecular and inter-molecular ligations of cohesive-ended and blunt-ended DNA were markedly stimulated by HMG1 and 2. Recombinant HMG2-domain A, B, and (A + B) polypeptides were similarly, but non-identically, effective for the stimulation of DSB ligation reaction. Ligation of single-strand breaks (nicks) was only slightly activated by the HMG proteins. The DNA end-**binding Ku** protein singly or in combination with the catalytic component of DNA-dependent protein kinase (**DNA-PK**) as the **DNA-PK** holoenzyme was ineffective for the ligation of linearized pUC119 DNA. Although the stimulatory effect of HMG1 and 2 on ligation of DSB in vitro was not specific to **DNA ligase IV**, these results suggest that HMG1 and 2 are involved in the final ligation step in DNA end-joining processes of DSB repair and V(D)J recombination.

L49 ANSWER 11 OF 45 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:244544 CAPLUS
DOCUMENT NUMBER: 135:3963
TITLE: Deficient DNA end joining activity in extracts from Fanconi anemia fibroblasts
AUTHOR(S): Lundberg, Richard; Mavinakere, Manohara; Campbell, Colin
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN, 55455, USA
SOURCE: Journal of Biological Chemistry (2001), 276(12), 9543-9549
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fanconi anemia (FA) is a genetic disorder assocd. with genomic instability and cancer predisposition. Cultured cells from FA patients display a high level of spontaneous chromosome breaks and an increased frequency of intragenic deletions, suggesting that FA cells may have deficiencies in properly processing DNA double strand breaks. In this study, an in vitro plasmid DNA end joining assay was used to characterize the end joining capabilities of nuclear exts. from diploid FA fibroblasts from complementation groups A, C, and D. The Fanconi anemia exts. had 3-9-fold less DNA end joining activity and rejoined substrates with significantly less fidelity than normal exts. Wild-type end joining activity could be reconstituted by mixing FA-D exts. with FA-A or FA-C exts., while mixing FA-A and FA-C exts. had no effect on end joining activity. Protein expression levels of the DNA-dependent protein kinase (**DNA-PK**)/**Ku**-dependent nonhomologous DNA end-joining proteins **Xrcc4**, **DNA ligase IV**, Ku70, and Ku86 in FA and normal exts. were indistinguishable, as were DNA-dependent protein kinase and DNA end **binding** activities. The end joining activity as measured by the assay was not sensitive to the **DNA-PK** inhibitor wortmannin or dependent on the nonhomologous DNA end-joining factor **Xrcc4**. However, when DNA/protein ratios were lowered, the end joining activity became wortmannin-sensitive and no difference in end joining activity was obsd. between normal and FA exts. Taken together, these results suggest that the FA fibroblast exts. have a deficiency in a DNA end joining process that is distinct from the **DNA-PK/Ku**-dependent nonhomologous DNA end joining pathway.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 12 OF 45 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:627731 CAPLUS
DOCUMENT NUMBER: 133:330376
TITLE: Interactions of the **DNA ligase IV-XRCC4** complex with DNA ends and the DNA-dependent protein kinase
AUTHOR(S): Chen, Ling; Trujillo, Kelly; Sung, Patrick; Tomkinson, Alan E.
CORPORATE SOURCE: Department of Molecular Medicine, Institute of Biotechnology, University of Texas Health Sciences Center, San Antonio, TX, 78245, USA
SOURCE: Journal of Biological Chemistry (2000), 275(34), 26196-26205
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The DNA-dependent protein kinase (**DNA-PK**), consisting of **Ku** and the **DNA-PK** catalytic subunit (DNA-PKcs), and the **DNA ligase IV-XRCC4** complex function together in the repair of DNA double-strand breaks by non-homologous end joining. These protein complexes are also required for the completion of V(D)J recombination events in immune cells. Here we demonstrate that the **DNA ligase IV-XRCC4** complex binds specifically to the ends of duplex DNA mols. and can act as a bridging factor, linking together duplex DNA mols. with complementary but non-ligatable ends. Although the DNA end-**binding** protein **Ku** inhibited DNA joining by **DNA ligase IV-XRCC4**, it did not prevent this complex from **binding** to DNA. Instead, **DNA ligase IV-XRCC4** and **Ku** bound simultaneously to the ends of duplex DNA mols. **DNA ligase IV-XRCC4** and DNA-PKcs also formed complexes at the ends of DNA mols., but DNA-PKcs did not inhibit ligation. Interestingly, DNA-PKcs stimulated intermol. ligation by **DNA ligase IV-XRCC4**. In the presence of **DNA-PK**, the majority of the joining events catalyzed by **DNA ligase IV-XRCC4** were intermol. because **Ku** inhibited intramol. ligation, but DNA-PKcs still stimulated intramol. ligation. We suggest that DNA-PKcs-contg. complexes formed at DNA ends enhance the assocn. of DNA ends via protein-protein interactions, thereby stimulating intermol. ligation.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 13 OF 45 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:355158 CAPLUS
DOCUMENT NUMBER: 131:154942
TITLE: Isolation of Ku70-**binding** proteins (KUBs)
AUTHOR(S): Yang, Chin-Rang; Yeh, Shuyuan; Leskov, Konstantin; Odegaard, Eric; Hsu, Hsin-Ling; Chang, Chawnshang; Kinsella, Timothy J.; Chen, David J.; Boothman, David A.
CORPORATE SOURCE: Department of Radiation Oncology and Department of Pharmacology and the Ireland Cancer Center, Laboratory of Molecular Stress Responses, Case Western Reserve University, Cleveland, OH, 44106-4942, USA
SOURCE: Nucleic Acids Research (1999), 27(10), 2165-2174
CODEN: NARHAD; ISSN: 0305-1048
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal

LANGUAGE: English

AB DNA-dependent protein kinase (**DNA-PK**) plays a crit. role in resealing DNA double-stand breaks by non-homologous end joining. Aside from **DNA-PK**, **XRCC4** and **DNA ligase IV**, other proteins which play a role(s) in this repair pathway remain unknown; **DNA-PK** contains a catalytic subunit (DNA-PKcs) and a DNA **binding** subunit (Ku70 and Ku80). The authors isolated Ku70-**binding** proteins (KUB1-KUB4) using yeast two-hybrid analyses. Sequence analyses revealed KUB1 to be apolipoprotein J (apoJ), also known as x-ray-inducible transcript 8 (XIP8), testosterone-repressed prostate message-2 (TRPM-2) and clusterin. KUB2 is Ku80. KUB3 and KUB4 are unknown, >10 kb transcripts. Interactions of apoJ/XIP8 or KUB3 with Ku70 were confirmed by co-immunopptn. analyses in MCF-7:WS8 breast cancer or IMR-90 normal lung fibroblast cells, resp. The interaction of apoJ/ XIP8 with Ku70 was confirmed by far-western analyses. Stable over-expression of full-length apoJ/XIP8 in MCF-7:WS8 caused decreased Ku70/Ku80 DNA end **binding** that was restored by apoJ/XIP8 monoclonal antibodies. The role of apoJ/XIP8 in ionizing radiation resistance/sensitivity is under investigation.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 14 OF 45 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:311882 CAPLUS

DOCUMENT NUMBER: 129:78006

TITLE: Non-histone chromosomal proteins HMG1 and 2 enhance ligation reaction of DNA double-strand breaks

AUTHOR(S): Nagaki, Sumiko; Yamamoto, Mayumi; Yumoto, Yoshiko; Shirakawa, Hitoshi; Yoshida, Michiteru; Teraoka, Hirobumi

CORPORATE SOURCE: Department of Pathological Biochemistry, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan

SOURCE: Biochemical and Biophysical Research Communications (1998), 246(1), 137-141
CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **DNA ligase IV** in a complex with **XRCC4** is responsible for DNA end-joining in repair of DNA double-strand breaks (DSB) and V(D)J recombination. We found that non-histone chromosomal high mobility group (HMG) proteins 1 and 2 enhanced the ligation of linearized pUC119 DNA with **DNA ligase IV** from rat liver nuclear ext. Intra-mol. and intermol. ligations of cohesive-ended and blunt-ended DNA were markedly stimulated by HMG1 and 2. Recombinant HMG2-domain A, B, and (A + B) polypeptides were similarly, but non-identically, effective for the stimulation of the DSB ligation reaction. Ligation of single-strand breaks (nicks) was only slightly activated by the HMG proteins. The DNA end-**binding Ku** protein singly or in combination with the catalytic component of DNA-dependent protein kinase (**DNA-PK**) as the **DNA-PK** holoenzyme was ineffective for the ligation of linearized pUC119 DNA. Although the stimulatory effect of HMG1 and 2 on ligation of DSB in vitro was not specific to **DNA ligase IV**, these results suggest that HMG1 and 2 are involved in the final ligation step in the DNA end-joining processes of DSB repair and V(D)J recombination.

L49 ANSWER 15 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2002:376335 SCISEARCH

THE GENUINE ARTICLE: 546LC

TITLE: Specific interaction of IP6 with human Ku70/80, the DNA-**binding** subunit of **DNA-PK**

AUTHOR: Hanakahi L A; West S C (Reprint)
CORPORATE SOURCE: Canc Res UK, London Res Inst, Clare Hall Labs, S Mimms EN6 3LD, Herts, England (Reprint)
COUNTRY OF AUTHOR: England
SOURCE: EMBO JOURNAL, (15 APR 2002) Vol. 21, No. 8, pp. 2038-2044. Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND. ISSN: 0261-4189.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 34

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In eukaryotic cells, DNA double-strand breaks can be repaired by non-homologous end-joining, a process dependent upon Ku70/80, **XRCC4** and **DNA ligase IV**. In mammals, this process also requires DNA-PKcs, the catalytic subunit of the DNA-dependent protein kinase **DNA-PK**. Previously, inositol hexakisphosphate (IP6) was shown to be bound by **DNA-PK** and to stimulate **DNA-PK**-dependent end-joining in vitro. Here, we localize IP6 **binding** to the Ku70/80 subunits of **DNA-PK**, and show that **DNA-PK**, alone exhibits no detectable affinity for IP6. Moreover, proteolysis mapping of Ku70/80 in the presence and absence of IP6 indicates that **binding** alters the conformation of the Ku70/80 heterodimer. The yeast homologue of Ku70/80, yKu70/80, fails to bind IP6, indicating that the function of IP6 in non-homologous end-joining, like that of DNA-PKcs, is unique to the mammalian end-joining process.

L49 ANSWER 16 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:282405 SCISEARCH
THE GENUINE ARTICLE: 413HV
TITLE: Deficient DNA end joining activity in extracts from Fanconi anemia fibroblasts
AUTHOR: Lundberg R; Mavinakere M; Campbell C (Reprint)
CORPORATE SOURCE: Univ Minnesota, Sch Med, Dept Pharmacol, 6-120 Jackson Hall, 321 Church St SE, Minneapolis, MN 55455 USA (Reprint); Univ Minnesota, Sch Med, Dept Pharmacol, Minneapolis, MN 55455 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (23 MAR 2001) Vol. 276, No. 12, pp. 9543-9549. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Fanconi anemia (FA) is a genetic disorder associated with genomic instability and cancer predisposition. Cultured cells from FA patients display a high level of spontaneous chromosome breaks and an increased frequency of intragenic deletions, suggesting that FA cells may have deficiencies in properly processing DNA double strand breaks. In this study, an in vitro plasmid DNA end joining assay was used to characterize the end joining capabilities of nuclear extracts from diploid FA fibroblasts from complementation groups A, C, and D, The Fanconi anemia extracts had 3-9-fold less DNA end joining activity and rejoined substrates with significantly less fidelity than normal extracts. Wild-type end joining activity could be reconstituted by mixing FA-D extracts with FA-A or FA-C extracts, while mixing FA-A and FA-C extracts had no effect on end joining activity. Protein expression levels of the DNA-dependent protein kinase (**DNA-PK**)/**Ku**-dependent nonhomologous DNA end-joining proteins **Xrcc4**, **DNA ligase IV**, Ku70, and Ku86 in FA and normal extracts were indistinguishable, as were DNA-dependent protein kinase and

DNA end **binding** activities. The end joining activity as measured by the assay was not sensitive to the **DNA-PK** inhibitor wortmannin or dependent on the nonhomologous DNA end-joining factor **Xrcc4**, However, when DNA/protein ratios were lowered, the end joining activity became wortmannin-sensitive and no difference in end joining activity was observed between normal and FA extracts. Taken together, these results suggest that the FA fibroblast extracts have a deficiency in a DNA end joining process that is distinct from the **DNA-PK/Ku**-dependent nonhomologous DNA end joining pathway.

L49 ANSWER 17 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2000:666749 SCISEARCH
THE GENUINE ARTICLE: 348RF
TITLE: Interactions of the **DNA ligase IV-XRCC4** complex with DNA ends and the DNA-dependent protein kinase
AUTHOR: Chen L; Trujillo K; Sung P; Tomkinson A E (Reprint)
CORPORATE SOURCE: UNIV TEXAS, HLTH SCI CTR, INST BIOTECHNOL, DEPT MOL MED, 15355 LAMBDA DR, SAN ANTONIO, TX 78245 (Reprint); UNIV TEXAS, HLTH SCI CTR, INST BIOTECHNOL, DEPT MOL MED, SAN ANTONIO, TX 78245
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (25 AUG 2000) Vol. 275, No. 34, pp. 26196-26205.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 45

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The DNA-dependent protein kinase (**DNA-PK**), consisting of **Ku** and the **DNA-PK** catalytic subunit (DNA-PKcs), and the **DNA ligase IV-XRCC4** complex function together in the repair of DNA double-strand breaks by non-homologous end joining. These protein complexes are also required for the completion of V(D)J recombination events in immune cells, Here we demonstrate that the **DNA ligase IV-XRCC4** complex binds specifically to the ends of duplex DNA molecules and can act as a bridging factor, linking together duplex DNA molecules with complementary but non-ligatable ends. Although the DNA end-**binding** protein **Ku** inhibited DNA joining by **DNA ligase IV-XRCC4**, it did not prevent this complex from **binding** to DNA, Instead, DNA ligase TVXRCC4 and **Ku** bound simultaneously to the ends of duplex DNA molecules. DNA ligase TV-**XRCC4** and DNA-PKcs also formed complexes at the ends of DNA molecules, but DNA-PKcs did not inhibit ligation, Interestingly, DNA-PKcs stimulated intermolecular ligation by DNA ligase TV-**XRCC4** , In the presence of **DNA-PK**, the majority of the joining events catalyzed by **DNA ligase IV-XRCC4** were intermolecular because **Ku** inhibited intramolecular ligation, but DNA-PKcs still stimulated intramolecular ligation, We suggest that DNA-PKcs-containing complexes formed at DNA ends enhance the association of DNA ends via protein-protein interactions, thereby stimulating intermolecular ligation.

L49 ANSWER 18 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:232199 BIOSIS
DOCUMENT NUMBER: PREV200100232199
TITLE: Deficient DNA end joining activity in extracts from Fanconi anemia fibroblasts.
AUTHOR(S): Lundberg, Richard; Mavinakere, Manohara; Campbell, Colin (1)

CORPORATE SOURCE: (1) Dept. of Pharmacology, University of Minnesota Medical School, 321 Church St., SE, 6-120 Jackson Hall, Minneapolis, MN, 55455: campb034@maroon.tc.umn.edu USA
SOURCE: Journal of Biological Chemistry, (March 23, 2001) Vol. 276, No. 12, pp. 9543-9549. print.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Fanconi anemia (FA) is a genetic disorder associated with genomic instability and cancer predisposition. Cultured cells from FA patients display a high level of spontaneous chromosome breaks and an increased frequency of intragenic deletions, suggesting that FA cells may have deficiencies in properly processing DNA double strand breaks. In this study, an in vitro plasmid DNA end joining assay was used to characterize the end joining capabilities of nuclear extracts from diploid FA fibroblasts from complementation groups A, C, and D. The Fanconi anemia extracts had 3-9-fold less DNA end joining activity and rejoined substrates with significantly less fidelity than normal extracts. Wild-type end joining activity could be reconstituted by mixing FA-D extracts with FA-A or FA-C extracts, while mixing FA-A and FA-C extracts had no effect on end joining activity. Protein expression levels of the DNA-dependent protein kinase (**DNA-PK**)/**Ku** -dependent nonhomologous DNA end-joining proteins **Xrcc4**, **DNA ligase IV**, Ku70, and Ku86 in FA and normal extracts were indistinguishable, as were DNA-dependent protein kinase and DNA end **binding** activities. The end joining activity as measured by the assay was not sensitive to the **DNA-PK** inhibitor wortmannin or dependent on the nonhomologous DNA end-joining factor **Xrcc4**. However, when DNA/protein ratios were lowered, the end joining activity became wortmannin-sensitive and no difference in end joining activity was observed between normal and FA extracts. Taken together, these results suggest that the FA fibroblast extracts have a deficiency in a DNA end joining process that is distinct from the **DNA-PK/Ku**-dependent nonhomologous DNA end joining pathway.

L49 ANSWER 19 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:452646 BIOSIS
DOCUMENT NUMBER: PREV200000452646
TITLE: Interactions of the **DNA ligase IV-XRCC4** complex with DNA ends and the DNA-dependent protein kinase.
AUTHOR(S): Chen, Ling; Trujillo, Kelly; Sung, Patrick; Tomkinson, Alan E. (1)
CORPORATE SOURCE: (1) Dept. of Molecular Medicine, Inst. of Biotechnology, University of Texas Health Science Center, 15355 Lambda Dr., San Antonio, TX, 78245 USA
SOURCE: Journal of Biological Chemistry, (August 25, 2000) Vol. 275, No. 34, pp. 26196-26205. print.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The DNA-dependent protein kinase (**DNA-PK**), consisting of **Ku** and the **DNA-PK** catalytic subunit (DNA-PKcs), and the **DNA ligase IV-XRCC4** complex function together in the repair of DNA double-strand breaks by non-homologous end joining. These protein complexes are also required for the completion of V(D)J recombination events in immune cells. Here we demonstrate that the **DNA ligase IV-XRCC4** complex binds specifically to the ends of duplex DNA molecules and can act as a bridging factor, linking together duplex DNA molecules with complementary but non-ligatable ends. Although the DNA end-**binding** protein **Ku** inhibited DNA joining by **DNA**

ligase IV-XRCC4, it did not prevent this complex from **binding** to DNA. Instead, **DNA ligase IV-XRCC4** and **Ku** bound simultaneously to the ends of duplex DNA molecules. **DNA ligase IV-XRCC4** and DNA-PKcs also formed complexes at the ends of DNA molecules, but DNA-PKcs did not inhibit ligation. Interestingly, DNA-PKcs stimulated intermolecular ligation by **DNA ligase IV-XRCC4**. In the presence of **DNA-PK**, the majority of the joining events catalyzed by **DNA ligase IV-XRCC4** were intermolecular because **Ku** inhibited intramolecular ligation, but DNA-PKcs still stimulated intramolecular ligation. We suggest that DNA-PKcs-containing complexes formed at DNA ends enhance the association of DNA ends via protein-protein interactions, thereby stimulating intermolecular ligation.

L49 ANSWER 20 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:266551 BIOSIS
DOCUMENT NUMBER: PREV199800266551
TITLE: Non-histone chromosomal proteins HMG1 and 2 enhance ligation reaction of DNA double-strand breaks.
AUTHOR(S): Nagaki, Sumiko; Yamamoto, Mayumi; Yumoto, Yoshiko; Shirakawa, Hitoshi; Yoshida, Michiteru; Teraoka, Hirobumi (1)
CORPORATE SOURCE: (1) Dep. Pathol. Biochem., Med. Res. Inst., Tokyo Med. Dental Univ., Chiyoda-ku, Tokyo 101-0062 Japan
SOURCE: Biochemical and Biophysical Research Communications, (May 8, 1998) Vol. 246, No. 1, pp. 137-141.
ISSN: 0006-291X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB **DNA ligase IV** in a complex with **XRCC4** is responsible for DNA end-joining in repair of DNA double-strand breaks (DSB) and V(D)J recombination. We found that non-histone chromosomal high mobility group (HMG) proteins 1 and 2 enhanced the ligation of linearized pUC119 DNA with **DNA ligase IV** from rat liver nuclear extract. Intra-molecular and intermolecular ligations of cohesive-ended and blunt-ended DNA were markedly stimulated by HMG1 and 2. Recombinant HMG2-domain A, B, and (A + B) polypeptides were similarly, but non-identically, effective for the stimulation of DSB ligation reaction. Ligation of single-strand breaks (nicks) was only slightly activated by the HMG proteins. The DNA end-**binding Ku** protein singly or in combination with the catalytic component of DNA-dependent protein kinase (DNAPK) as the **DNA-PK** holoenzyme was ineffective for the ligation of linearized pUC119 DNA. Although the stimulatory effect of HMG1 and 2 on ligation of DSB in vitro was not specific to **DNA ligase IV**, these results suggest that HMG1 and 2 are involved in the final ligation step in DNA end-joining processes of DSB repair and V(D)J recombination.

L49 ANSWER 21 OF 45 LIFESCI COPYRIGHT 2002 CSA
ACCESSION NUMBER: 2001:44836 LIFESCI
TITLE: Deficient DNA End Joining Activity in Extracts from Fanconi Anemia Fibroblasts
AUTHOR: Lundberg, R.; Mavinakere, M.; Campbell, C.
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota Medical School, Minneapolis, Minnesota 55455; E-mail: campb034@maroon.tc.umn.edu
SOURCE: Journal of Biological Chemistry [J. Biol. Chem.], (20010323) vol. 276, no. 12, pp. 9543-9549.
ISSN: 0021-9258.
DOCUMENT TYPE: Journal
FILE SEGMENT: N
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Fanconi anemia (FA) is a genetic disorder associated with genomic instability and cancer predisposition. Cultured cells from FA patients display a high level of spontaneous chromosome breaks and an increased frequency of intragenic deletions, suggesting that FA cells may have deficiencies in properly processing DNA double strand breaks. In this study, an in vitro plasmid DNA end joining assay was used to characterize the end joining capabilities of nuclear extracts from diploid FA fibroblasts from complementation groups A, C, and D. The Fanconi anemia extracts had 3-9-fold less DNA end joining activity and rejoined substrates with significantly less fidelity than normal extracts. Wild-type end joining activity could be reconstituted by mixing FA-D extracts with FA-A or FA-C extracts, while mixing FA-A and FA-C extracts had no effect on end joining activity. Protein expression levels of the DNA-dependent protein kinase (**DNA-PK**)/**Ku** -dependent nonhomologous DNA end-joining proteins **Xrcc4**, **DNA ligase IV**, Ku70, and Ku86 in FA and normal extracts were indistinguishable, as were DNA-dependent protein kinase and DNA end **binding** activities. The end joining activity as measured by the assay was not sensitive to the **DNA-PK** inhibitor wortmannin or dependent on the nonhomologous DNA end-joining factor **Xrcc4**. However, when DNA/protein ratios were lowered, the end joining activity became wortmannin-sensitive and no difference in end joining activity was observed between normal and FA extracts. Taken together, these results suggest that the FA fibroblast extracts have a deficiency in a DNA end joining process that is distinct from the **DNA-PK**/**Ku**-dependent nonhomologous DNA end joining pathway.

L49 ANSWER 22 OF 45 LIFESCI COPYRIGHT 2002 CSA

ACCESSION NUMBER: 2000:118195 LIFESCI

TITLE: Interactions of the **DNA Ligase IV-XRCC4** Complex with DNA Ends and the DNA-dependent Protein Kinase

AUTHOR: Chen, L.; Trujillo, K.; Sung, P.; Tomkinson, A.E.

CORPORATE SOURCE: Department of Molecular Medicine, Institute of Biotechnology, University of Texas Health Science Center, San Antonio, Texas 78245; E-mail: Tomkinson@uthscsa.edu

SOURCE: Journal of Biological Chemistry [J. Biol. Chem.], (20000825) vol. 275, no. 34, pp. 26196-26205. ISSN: 0021-9258.

DOCUMENT TYPE: Journal

FILE SEGMENT: N

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The DNA-dependent protein kinase (**DNA-PK**), consisting of **Ku** and the **DNA-PK** catalytic subunit (DNA-PKcs), and the **DNA ligase IV-XRCC4** complex function together in the repair of DNA double-strand breaks by non-homologous end joining. These protein complexes are also required for the completion of V(D)J recombination events in immune cells. Here we demonstrate that the **DNA ligase IV-XRCC4** complex binds specifically to the ends of duplex DNA molecules and can act as a bridging factor, linking together duplex DNA molecules with complementary but non-ligatable ends. Although the DNA end-**binding** protein **Ku** inhibited DNA joining by **DNA ligase IV- XRCC4**, it did not prevent this complex from **binding** to DNA. Instead, **DNA ligase IV-XRCC4** and **Ku** bound simultaneously to the ends of duplex DNA molecules. **DNA ligase IV-XRCC4** and DNA-PKcs also formed complexes at the ends of DNA molecules, but DNA-PKcs did not inhibit ligation. Interestingly, DNA-PKcs stimulated intermolecular ligation by **DNA ligase IV-XRCC4**. In the presence of **DNA-PK**, the majority of the joining events

catalyzed by **DNA ligase IV-XRCC4** were intermolecular because **Ku** inhibited intramolecular ligation, but DNA-PKcs still stimulated intramolecular ligation. We suggest that DNA-PKcs-containing complexes formed at DNA ends enhance the association of DNA ends via protein-protein interactions, thereby stimulating intermolecular ligation.

L49 ANSWER 23 OF 45 CANCERLIT
ACCESSION NUMBER: 2002150467 CANCERLIT
DOCUMENT NUMBER: 21950349 PubMed ID: 11953323
TITLE: Specific interaction of IP6 with human Ku70/80, the DNA-**binding** subunit of **DNA-PK**.
AUTHOR: Hanakahi Les A; West Stephen C
CORPORATE SOURCE: Cancer Research UK, London Research Institute, Clare Hall Laboratories, South Mimms, Hertfordshire EN6 3LD, UK.
SOURCE: EMBO JOURNAL, (2002 Apr 15) 21 (8) 2038-44.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 2002216939
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020726
Last Updated on STN: 20020726

AB In eukaryotic cells, DNA double-strand breaks can be repaired by non-homologous end-joining, a process dependent upon Ku70/80, **XRCC4** and **DNA ligase IV**. In mammals, this process also requires **DNA-PK**(cs), the catalytic subunit of the DNA-dependent protein kinase **DNA-PK**. Previously, inositol hexakisphosphate (IP6) was shown to be bound by **DNA-PK** and to stimulate **DNA-PK** -dependent end-joining in vitro. Here, we localize IP6 **binding** to the Ku70/80 subunits of **DNA- PK**, and show that **DNA-PK**(cs) alone exhibits no detectable affinity for IP6. Moreover, proteolysis mapping of Ku70/80 in the presence and absence of IP6 indicates that **binding** alters the conformation of the Ku70/80 heterodimer. The yeast homologue of Ku70/80, yKu70/80, fails to bind IP6, indicating that the function of IP6 in non-homologous end-joining, like that of **DNA-PK**(cs), is unique to the mammalian end-joining process.

L49 ANSWER 24 OF 45 CANCERLIT
ACCESSION NUMBER: 2001145441 CANCERLIT
DOCUMENT NUMBER: 21145441 PubMed ID: 11226171
TITLE: Novel functional requirements for non-homologous DNA end joining in Schizosaccharomyces pombe.
AUTHOR: Manolis K G; Nimmo E R; Hartsuiker E; Carr A M; Jeggo P A; Allshire R C
CORPORATE SOURCE: MRC Cell Mutation Unit, University of Sussex, Falmer, Sussex BN1, UK.
SOURCE: EMBO JOURNAL, (2001 Jan 15) 20 (1-2) 210-21.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 2001202768
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010515
Last Updated on STN: 20010515

AB DNA double strand break (DSB) repair by non-homologous end joining (NHEJ) in mammalian cells requires the Ku70-Ku80 heterodimer, the **DNA-PK** catalytic subunit DNA-PKcs, as well as **DNA ligase IV** and **Xrcc4**. NHEJ of plasmid DSBs in

Saccharomyces cerevisiae requires **Ku**, **Xrcc4** and **DNA ligase IV**, as well as Mre11, Rad50, Xrs2 and DNA damage checkpoint proteins. Saccharomyces cerevisiae **Ku** is also required for telomere length maintenance and transcriptional silencing. We have characterized NHEJ in Schizosaccharomyces pombe using an extrachromosomal assay and find that, as anticipated, it is Ku70 and **DNA ligase IV** dependent. Unexpectedly, we find that Rad32, Rad50 (the S.pombe homologues of Mre11 and Rad50, respectively) and checkpoint proteins are not required for NHEJ. Furthermore, although S.pombe Ku70 is required for maintenance of telomere length, it is dispensable for transcriptional silencing at telomeres and is located throughout the nucleus rather than concentrated at the telomeres. Together, these results provide insight into the mechanism of NHEJ and contrast significantly with recent studies in S.cerevisiae.

L49 ANSWER 25 OF 45 CANCERLIT
ACCESSION NUMBER: 1999238412 CANCERLIT
DOCUMENT NUMBER: 99238412 PubMed ID: 10219089
TITLE: Isolation of Ku70-**binding** proteins (KUBs).
AUTHOR: Yang C R; Yeh S; Leskov K; Odegaard E; Hsu H L; Chang C; Kinsella T J; Chen D J; Boothman D A
CORPORATE SOURCE: Department of Radiation Oncology and Department of Pharmacology and the Ireland Cancer Center,Laboratory of Molecular Stress Responses, Case Western Reserve University, BRB-326 East,10900 Euclid Avenue, Cleveland, OH 44106-4942, USA.
CONTRACT NUMBER: CA-50595 (NCI)
CA-ES78530 (NCI)
CA50519 (NCI)
SOURCE: NUCLEIC ACIDS RESEARCH, (1999 May 15) 27 (10) 2165-74. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 1999238412
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990709
Last Updated on STN: 20020726
AB DNA-dependent protein kinase (**DNA-PK**) plays a critical role in resealing DNA double-stand breaks by non-homologous end joining. Aside from **DNA-PK**, **XRCC4** and **DNA ligase IV**, other proteins which play a role(s) in this repair pathway remain unknown; **DNA-PK** contains a catalytic subunit (DNA-PKcs) and a DNA **binding** subunit (Ku70 and Ku80). We isolated Ku70-**binding** proteins (KUB1-KUB4) using yeast two-hybrid analyses. Sequence analyses revealed KUB1 to be apolipoprotein J (apoJ), also known as X-ray-inducible transcript 8 (XIP8), testosterone-repressed prostate message-2 (TRPM-2) and clusterin. KUB2 is Ku80. KUB3 and KUB4 are unknown, >10 kb trans-cripts. Interactions of apoJ/XIP8 or KUB3 with Ku70 were confirmed by co-immunoprecipitation analyses in MCF-7:WS8 breast cancer or IMR-90 normal lung fibroblast cells, respectively. The interaction of apoJ/XIP8 with Ku70 was confirmed by far-western analyses. Stable over-expression of full-length apoJ/XIP8 in MCF-7:WS8 caused decreased Ku70/Ku80 DNA end **binding** that was restored by apoJ/XIP8 monoclonal antibodies. The role of apoJ/XIP8 in ionizing radiation resistance/sensitivity is under investigation.

L49 ANSWER 26 OF 45 CANCERLIT
ACCESSION NUMBER: 1998342672 CANCERLIT
DOCUMENT NUMBER: 98342672 PubMed ID: 9677708
TITLE: DNA breakage and repair.
AUTHOR: Jeggo P A
CORPORATE SOURCE: MRC Cell Mutation Unit, University of Sussex, Brighton, United Kingdom.

SOURCE: ADVANCES IN GENETICS, (1998) 38 185-218. Ref: 152
Journal code: 0370421. ISSN: 0065-2660.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 1998342672
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980910
Last Updated on STN: 20020726

AB For many years it has been evident that mammalian cells differ dramatically from yeast and rejoin the majority of their DNA DSBs by a nonhomologous mechanism, recently termed NHEJ. In the last few years a number of genes and proteins have been identified that operate in the pathway providing insights into the mechanism. These proteins include the three components of **DNA-PK, DNA ligase IV**, and **XRCC4**. In yeast Sir2, -3, and -4 proteins are also involved in the process and therefore are likely to play a role in higher organisms. Studies with yeast suggest that NHEJ is an error-free mechanism. Although the process is far from understood, it is likely that the **DNA-PK** complex or **Ku** alone acts in a complex with the Sir proteins possibly protecting the ends and preventing random rejoining. Further work is required to establish the details of this mechanism and to determine whether this represents an accurate rejoining process for a complex break induced by ionizing radiation. It will be intriguing to discover how the cell achieves efficient and accurate rejoining without the use of homology. Interactions between the components of **DNA-PK** and other proteins playing a central role in damage response mechanisms are beginning to emerge. Interestingly, there is evidence that DNA repair and damage response mechanisms overlap in lower organisms. The overlapping defects of the yeast **Ku** mutants, tell mutants, and AT cell lines in telomere maintenance further suggest overlapping functions or interacting mechanisms. A challenge for the future will be to establish how these different damage response mechanisms overlap and interact.

L49 ANSWER 27 OF 45 CANCERLIT
ACCESSION NUMBER: 1998262931 CANCERLIT
DOCUMENT NUMBER: 98262931 PubMed ID: 9600082
TITLE: Non-histone chromosomal proteins HMG1 and 2 enhance ligation reaction of DNA double-strand breaks.
AUTHOR: Nagaki S; Yamamoto M; Yumoto Y; Shirakawa H; Yoshida M; Teraoka H
CORPORATE SOURCE: Department of Pathological Biochemistry, Tokyo Medical and Dental University, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 May 8) 246 (1) 137-41.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 1998262931
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980713
Last Updated on STN: 20020726

AB **DNA ligase IV** in a complex with **XRCC4** is responsible for DNA end-joining in repair of DNA double-strand breaks (DSB) and V(D)J recombination. We found that non-histone chromosomal high mobility group (HMG) proteins 1 and 2 enhanced the ligation of linearized pUC119 DNA with **DNA ligase IV** from rat liver nuclear extract. Intra-molecular and inter-molecular ligations of cohesive-ended and

blunt-ended DNA were markedly stimulated by HMG1 and 2. Recombinant HMG2-domain A, B, and (A + B) polypeptides were similarly, but non-identically, effective for the stimulation of DSB ligation reaction. Ligation of single-strand breaks (nicks) was only slightly activated by the HMG proteins. The DNA end-**binding Ku** protein singly or in combination with the catalytic component of DNA-dependent protein kinase (**DNA-PK**) as the **DNA-PK** holoenzyme was ineffective for the ligation of linearized pUC119 DNA. Although the stimulatory effect of HMG1 and 2 on ligation of DSB in vitro was not specific to **DNA ligase IV**, these results suggest that HMG1 and 2 are involved in the final ligation step in DNA end-joining processes of DSB repair and V(D)J recombination.

L49 ANSWER 28 OF 45 Elsevier BIOBASE COPYRIGHT 2002 Elsevier Science B.V.
ACCESSION NUMBER: 2000204476 Elsevier BIOBASE
TITLE: Interactions of the **DNA ligase IV-XRCC4** complex with DNA ends and the DNA-dependent protein kinase
AUTHOR: Chen L.; Trujillo K.; Sung P.; Tomkinson A.E.
CORPORATE SOURCE: A.E. Tomkinson, Dept. of Molecular Medicine, Inst. of Biotechnology, Univ. of Texas Health Science Center, 15355 Lambda Dr., San Antonio, TX 78245, United States.
E-mail: Tomkinson@uthscsa.edu
SOURCE: Journal of Biological Chemistry, (25 AUG 2000), 275/34 (26196-26205), 47 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The DNA-dependent protein kinase (**DNA-PK**), consisting of **Ku** and the **DNA-PK** catalytic subunit (DNA-PKcs), and the **DNA ligase IV-XRCC4** complex function together in the repair of DNA double-strand breaks by non-homologous end joining. These protein complexes are also required for the completion of V(D)J recombination events in immune cells. Here we demonstrate that the **DNA ligase IV-XRCC4** complex binds specifically to the ends of duplex DNA molecules and can act as a bridging factor, linking together duplex DNA molecules with complementary but non-ligatable ends. Although the DNA end-**binding** protein **Ku** inhibited DNA joining by **DNA ligase IV-XRCC4**, it did not prevent this complex from **binding** to DNA. Instead, **DNA ligase IV-XRCC4** and **Ku** bound simultaneously to the ends of duplex DNA molecules. **DNA ligase IV-XRCC4** and DNA-PKcs also formed complexes at the ends of DNA molecules, but DNA-PKcs did not inhibit ligation. Interestingly, DNA-PKcs stimulated intermolecular ligation by **DNA ligase IV-XRCC4**. In the presence of **DNA-PK**, the majority of the joining events catalyzed by **DNA ligase IV-XRCC4** were intermolecular because **Ku** inhibited intramolecular ligation, but DNA-PKcs still stimulated intramolecular ligation. We suggest that DNA-PKcs-containing complexes formed at DNA ends enhance the association of DNA ends via protein-protein interactions, thereby stimulating intermolecular ligation.

L49 ANSWER 29 OF 45 Elsevier BIOBASE COPYRIGHT 2002 Elsevier Science B.V.
ACCESSION NUMBER: 1998210395 Elsevier BIOBASE
TITLE: Non-histone chromosomal proteins HMG1 and 2 enhance ligation reaction of DNA double-strand breaks
AUTHOR: Nagaki S.; Yamamoto M.; Yumoto Y.; Shirakawa H.; Yoshida M.; Teraoka H.

CORPORATE SOURCE: H. Teraoka, Department Pathological Biochemistry, Medical Research Institute, Tokyo Medical and Dental University, Chiyoda-ku, Tokyo 101-0062, Japan. E-mail: hteraoka.pbc@mri.tmd.ac.jp
SOURCE: Biochemical and Biophysical Research Communications, (08 MAY 1998), 246/1 (137-141), 36 reference(s) CODEN: BBRCA0 ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **DNA ligase IV** in a complex with **XRCC4** is responsible for DNA end-joining in repair of DNA double-strand breaks (DSB) and V(D)J recombination. We found that non-histone chromosomal high mobility group (HMG) proteins 1 and 2 enhanced the ligation of linearized pUC119 DNA with **DNA ligase IV** from rat liver nuclear extract. Intra-molecular and inter-molecular ligations of cohesive-ended and blunt-ended DNA were markedly stimulated by HMG1 and 2. Recombinant HMG2-domain A, B, and (A + B) polypeptides were similarly, but non-identically, effective for the stimulation of DSB ligation reaction. Ligation of single-strand breaks (nicks) was only slightly activated by the HMG proteins. The DNA end-**binding Ku** protein singly or in combination with the catalytic component of DNA-dependent protein kinase (**DNA-PK**) as the **DNA-PK** holoenzyme was ineffective for the ligation of linearized pUC119 DNA. Although the stimulatory effect of HMG1 and 2 on ligation of DSB in vitro was not specific to **DNA ligase IV**, these results suggest that HMG1 and 2 are involved in the final ligation step in DNA end-joining processes of DSB repair and V(D)J recombination.

L49 ANSWER 30 OF 45 BIOTECHNO COPYRIGHT 2002 Elsevier Science B.V.
ACCESSION NUMBER: 2002:34800216 BIOTECHNO
TITLE: V(D)J recombination: RAG proteins, repair factors, and regulation
AUTHOR: Gellert M.
CORPORATE SOURCE: M. Gellert, Laboratory of Molecular Biology, N. Inst. Diabet./Digest./Kidney Dis., National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892-0540, United States. E-mail: gellert@helix.nih.gov
SOURCE: Annual Review of Biochemistry, (2002), 71/- (101-132), 207 reference(s) CODEN: ARBOAW ISSN: 0066-4154
DOCUMENT TYPE: Journal; General Review
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:34800216 BIOTECHNO
AB V(D)J recombination is the specialized DNA rearrangement used by cells of the immune system to assemble immunoglobulin and T-cell receptor genes from the preexisting gene segments. Because there is a large choice of segments to join, this process accounts for much of the diversity of the immune response. Recombination is initiated by the lymphoid-specific RAG1 and RAG2 proteins, which cooperate to make double-strand breaks at specific recognition sequences (recombination signal sequences, RSSs). The neighboring coding DNA is converted to a hairpin during breakage. Broken ends are then processed and joined with the help of several factors also involved in repair of radiation-damaged DNA, including the DNA-dependent protein kinase (**DNA-PK**) and the **Ku**, Artemis, **DNA ligase IV**, and **Xrcc4** proteins, and possibly histone H2AX and the Mre11/Rad50/Nbs1 complex. There may be other factors not yet known. V(D)J recombination is strongly regulated by limiting access to RSS sites

within chromatin, so that particular sites are available only in certain cell types and developmental stages. The roles of enhancers, histone acetylation, and chromatin remodeling factors in controlling accessibility are discussed. The RAG proteins are also capable of transposing RSS-ended fragments into new DNA sites. This transposition helps to explain the mechanism of RAG action and supports earlier proposals that V(D)J recombination evolved from an ancient mobile DNA element.

L49 ANSWER 31 OF 45 BIOTECHNO COPYRIGHT 2002 Elsevier Science B.V.
ACCESSION NUMBER: 2000:30676666 BIOTECHNO
TITLE: Interactions of the **DNA ligase IV-XRCC4** complex with DNA ends and the DNA-dependent protein kinase
AUTHOR: Chen L.; Trujillo K.; Sung P.; Tomkinson A.E.
CORPORATE SOURCE: A.E. Tomkinson, Dept. of Molecular Medicine, Inst. of Biotechnology, Univ. of Texas Health Science Center, 15355 Lambda Dr., San Antonio, TX 78245, United States.
E-mail: Tomkinson@uthscsa.edu
SOURCE: Journal of Biological Chemistry, (25 AUG 2000), 275/34 (26196-26205), 47 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30676666 BIOTECHNO
AB The DNA-dependent protein kinase (**DNA-PK**), consisting of **Ku** and the **DNA-PK** catalytic subunit (DNA-PKcs), and the **DNA ligase IV-XRCC4** complex function together in the repair of DNA double-strand breaks by non-homologous end joining. These protein complexes are also required for the completion of V(D)J recombination events in immune cells. Here we demonstrate that the **DNA ligase IV-XRCC4** complex binds specifically to the ends of duplex DNA molecules and can act as a bridging factor, linking together duplex DNA molecules with complementary but non-ligatable ends. Although the DNA end-**binding** protein **Ku** inhibited DNA joining by **DNA ligase IV-XRCC4**, it did not prevent this complex from **binding** to DNA. Instead, **DNA ligase IV-XRCC4** and **Ku** bound simultaneously to the ends of duplex DNA molecules. **DNA ligase IV-XRCC4** and DNA-PKcs also formed complexes at the ends of DNA molecules, but DNA-PKcs did not inhibit ligation. Interestingly, DNA-PKcs stimulated intermolecular ligation by **DNA ligase IV-XRCC4**. In the presence of **DNA-PK**, the majority of the joining events catalyzed by **DNA ligase IV-XRCC4** were intermolecular because **Ku** inhibited intramolecular ligation, but DNA-PKcs still stimulated intramolecular ligation. We suggest that DNA-PKcs-containing complexes formed at DNA ends enhance the association of DNA ends via protein-protein interactions, thereby stimulating intermolecular ligation.

L49 ANSWER 32 OF 45 BIOTECHNO COPYRIGHT 2002 Elsevier Science B.V.
ACCESSION NUMBER: 1998:28413941 BIOTECHNO
TITLE: Non-histone chromosomal proteins HMG1 and 2 enhance ligation reaction of DNA double-strand breaks
AUTHOR: Nagaki S.; Yamamoto M.; Yumoto Y.; Shirakawa H.; Yoshida M.; Teraoka H.
CORPORATE SOURCE: H. Teraoka, Department Pathological Biochemistry, Medical Research Institute, Tokyo Medical and Dental University, Chiyoda-ku, Tokyo 101-0062, Japan.

E-mail: hteraoka.pbc@mri.tmd.ac.jp
SOURCE: Biochemical and Biophysical Research Communications, (08 MAY 1998), 246/1 (137-141), 36 reference(s)
CODEN: BBRCA0 ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:28413941 BIOTECHNO
AB **DNA ligase IV** in a complex with **XRCC4** is responsible for DNA end-joining in repair of DNA double-strand breaks (DSB) and V(D)J recombination. We found that non-histone chromosomal high mobility group (HMG) proteins 1 and 2 enhanced the ligation of linearized pUC119 DNA with **DNA ligase IV** from rat liver nuclear extract. Intra-molecular and inter-molecular ligations of cohesive-ended and blunt-ended DNA were markedly stimulated by HMG1 and 2. Recombinant HMG2-domain A, B, and (A + B) polypeptides were similarly, but non-identically, effective for the stimulation of DSB ligation reaction. Ligation of single-strand breaks (nicks) was only slightly activated by the HMG proteins. The DNA end-**binding Ku** protein singly or in combination with the catalytic component of DNA-dependent protein kinase (**DNA-PK**) as the **DNA-PK** holoenzyme was ineffective for the ligation of linearized pUC119 DNA. Although the stimulatory effect of HMG1 and 2 on ligation of DSB in vitro was not specific to **DNA ligase IV**, these results suggest that HMG1 and 2 are involved in the final ligation step in DNA end-joining processes of DSB repair and V(D)J recombination.

L49 ANSWER 33 OF 45 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002265621 EMBASE
TITLE: V(D)J recombination: RAG proteins, repair factors, and regulation.
AUTHOR: Gellert M.
CORPORATE SOURCE: M. Gellert, Laboratory of Molecular Biology, N. Inst. Diabet./Digest./Kidney Dis., National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892-0540, United States. gellert@helix.nih.gov
SOURCE: Annual Review of Biochemistry, (2002) 71/- (101-132).
Refs: 207
ISSN: 0066-4154 CODEN: ARBOAW
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB V(D)J recombination is the specialized DNA rearrangement used by cells of the immune system to assemble immunoglobulin and T-cell receptor genes from the preexisting gene segments. Because there is a large choice of segments to join, this process accounts for much of the diversity of the immune response. Recombination is initiated by the lymphoid-specific RAG1 and RAG2 proteins, which cooperate to make double-strand breaks at specific recognition sequences (recombination signal sequences, RSSs). The neighboring coding DNA is converted to a hairpin during breakage. Broken ends are then processed and joined with the help of several factors also involved in repair of radiation-damaged DNA, including the DNA-dependent protein kinase (**DNA-PK**) and the **Ku**, Artemis, **DNA ligase IV**, and **Xrcc4** proteins, and possibly histone H2AX and the Mre11/Rad50/Nbs1 complex. There may be other factors not yet known. V(D)J recombination is strongly regulated by limiting access to RSS sites within chromatin, so that particular sites are available only in certain cell types and developmental stages. The roles of enhancers, histone acetylation, and chromatin remodeling factors in controlling accessibility are discussed. The RAG proteins are also

capable of transposing RSS-ended fragments into new DNA sites. This transposition helps to explain the mechanism of RAG action and supports earlier proposals that V(D)J recombination evolved from an ancient mobile DNA element.

L49 ANSWER 34 OF 45 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000314297 EMBASE
TITLE: Interactions of the **DNA ligase IV-XRCC4** complex with DNA ends and the DNA-dependent protein kinase.
AUTHOR: Chen L.; Trujillo K.; Sung P.; Tomkinson A.E.
CORPORATE SOURCE: A.E. Tomkinson, Dept. of Molecular Medicine, Inst. of Biotechnology, Univ. of Texas Health Science Center, 15355 Lambda Dr., San Antonio, TX 78245, United States. Tomkinson@uthscsa.edu
SOURCE: Journal of Biological Chemistry, (25 Aug 2000) 275/34 (26196-26205).
Refs: 47
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The DNA-dependent protein kinase (**DNA-PK**), consisting of **Ku** and the **DNA-PK** catalytic subunit (DNA-PKcs), and the **DNA ligase IV-XRCC4** complex function together in the repair of DNA double-strand breaks by non-homologous end joining. These protein complexes are also required for the completion of V(D)J recombination events in immune cells. Here we demonstrate that the **DNA ligase IV-XRCC4** complex binds specifically to the ends of duplex DNA molecules and can act as a bridging factor, linking together duplex DNA molecules with complementary but non-ligatable ends. Although the DNA end-**binding** protein **Ku** inhibited DNA joining by **DNA ligase IV-XRCC4**, it did not prevent this complex from **binding** to DNA. Instead, **DNA ligase IV-XRCC4** and **Ku** bound simultaneously to the ends of duplex DNA molecules. **DNA ligase IV-XRCC4** and DNA-PKcs also formed complexes at the ends of DNA molecules, but DNA-PKcs did not inhibit ligation. Interestingly, DNA-PKcs stimulated intermolecular ligation by **DNA ligase IV-XRCC4**. In the presence of **DNA-PK**, the majority of the joining events catalyzed by **DNA ligase IV-XRCC4** were intermolecular because **Ku** inhibited intramolecular ligation, but DNA-PKcs still stimulated intramolecular ligation. We suggest that DNA-PKcs-containing complexes formed at DNA ends enhance the association of DNA ends via protein-protein interactions, thereby stimulating intermolecular ligation.

L49 ANSWER 35 OF 45 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998304342 EMBASE
TITLE: Non-histone chromosomal proteins HMG1 and 2 enhance ligation reaction of DNA double-strand breaks.
AUTHOR: Nagaki S.; Yamamoto M.; Yumoto Y.; Shirakawa H.; Yoshida M.; Teraoka H.
CORPORATE SOURCE: H. Teraoka, Department Pathological Biochemistry, Medical Research Institute, Tokyo Medical and Dental University, Chiyoda-ku, Tokyo 101-0062, Japan. hteraoka.pbc@mri.tmd.ac.jp
SOURCE: Biochemical and Biophysical Research Communications, (8 May 1998) 246/1 (137-141).
Refs: 36
ISSN: 0006-291X CODEN: BBRCA

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **DNA ligase IV** in a complex with **XRCC4** is responsible for DNA end-joining in repair of DNA double-strand breaks (DSB) and V(D)J recombination. We found that non-histone chromosomal high mobility group (HMG) proteins 1 and 2 enhanced the ligation of linearized pUC119 DNA with **DNA ligase IV** from rat liver nuclear extract. Intra-molecular and inter-molecular ligations of cohesive-ended and blunt-ended DNA were markedly stimulated by HMG1 and 2. Recombinant HMG2-domain A, B, and (A + B) polypeptides were similarly, but non-identically, effective for the stimulation of DSB ligation reaction. Ligation of single-strand breaks (nicks) was only slightly activated by the HMG proteins. The DNA end-**binding Ku** protein singly or in combination with the catalytic component of DNA-dependent protein kinase (**DNA-PK**) as the **DNA-PK** holoenzyme was ineffective for the ligation of linearized pUC119 DNA. Although the stimulatory effect of HMG1 and 2 on ligation of DSB in vitro was not specific to **DNA ligase IV**, these results suggest that HMG1 and 2 are involved in the final ligation step in DNA end-joining processes of DSB repair and V(D)J recombination.

L49 ANSWER 36 OF 45 TOXCENTER COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:31513 TOXCENTER
DOCUMENT NUMBER: 21145441 PubMed ID: 11226171
TITLE: Novel functional requirements for non-homologous DNA end joining in Schizosaccharomyces pombe
AUTHOR(S): Manolis K G; Nimmo E R; Hartsuiker E; Carr A M; Jeggo P A; Allshire R C
CORPORATE SOURCE: MRC Cell Mutation Unit, University of Sussex, Falmer, Sussex BN1, UK
SOURCE: EMBO JOURNAL, (2001 Jan 15) 20 (1-2) 210-21. Journal Code: 8208664. ISSN: 0261-4189.
COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 2001202768
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

AB DNA double strand break (DSB) repair by non-homologous end joining (NHEJ) in mammalian cells requires the Ku70-Ku80 heterodimer, the **DNA-PK** catalytic subunit DNA-PKcs, as well as **DNA ligase IV** and **Xrcc4**. NHEJ of plasmid DSBs in Saccharomyces cerevisiae requires **Ku**, **Xrcc4** and **DNA ligase IV**, as well as Mre11, Rad50, Xrs2 and DNA damage checkpoint proteins. Saccharomyces cerevisiae **Ku** is also required for telomere length maintenance and transcriptional silencing. We have characterized NHEJ in Schizosaccharomyces pombe using an extrachromosomal assay and find that, as anticipated, it is Ku70 and **DNA ligase IV** dependent. Unexpectedly, we find that Rad32, Rad50 (the S.pombe homologues of Mre11 and Rad50, respectively) and checkpoint proteins are not required for NHEJ. Furthermore, although S.pombe Ku70 is required for maintenance of telomere length, it is dispensable for transcriptional silencing at telomeres and is located throughout the nucleus rather than concentrated at the telomeres. Together, these results provide insight into the mechanism of NHEJ and contrast significantly with recent studies in S.cerevisiae.

L49 ANSWER 37 OF 45 TOXCENTER COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:63329 TOXCENTER

DOCUMENT NUMBER: 99415934 PubMed ID: 10485901
TITLE: Deletion of Ku86 causes early onset of senescence in mice
AUTHOR(S): Vogel H; Lim D S; Karsenty G; Finegold M; Hasty P
CORPORATE SOURCE: Department of Pathology, Baylor College of Medicine, Houston, TX 77030, USA
CONTRACT NUMBER: 1RO1CA76317-01 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Sep 14) 96 (19) 10770-5. Journal Code: 7505876. ISSN: 0027-8424.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 1999415934
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

AB DNA double-strand breaks formed during the assembly of antigen receptors or after exposure to ionizing radiation are repaired by proteins important for nonhomologous end joining that include Ku86, Ku70, **DNA-PK**(CS), **Xrcc4**, and **DNA ligase IV**. Here we show that ku86-mutant mice, compared with control littermates, prematurely exhibited age-specific changes characteristic of senescence that include osteopenia, atrophic skin, hepatocellular degeneration, hepatocellular inclusions, hepatic hyperplastic foci, and age-specific mortality. Cancer and likely sepsis (indicated by reactive immune responses) partly contributed to age-specific mortality for both cohorts, and both conditions occurred earlier in ku86(-/-) mice. These data indicate that Ku86-dependent chromosomal metabolism is important for determining the onset of age-specific changes characteristic of senescence in mice.

L49 ANSWER 38 OF 45 USPATFULL
ACCESSION NUMBER: 2002:235524 USPATFULL
TITLE: Inhibitors of alternative alleles of genes encoding products that mediate cell response to environmental changes
INVENTOR(S): Housman, David E., Newton, MA, UNITED STATES
Ledley, Fred D., Needham, MA, UNITED STATES
Stanton, Vincent P., JR., Belmont, MA, UNITED STATES
PATENT ASSIGNEE(S): Variagenics, Inc., a Delaware corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002127714	A1	20020912
APPLICATION INFO.:	US 2001-782837	A1	20010214 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-45054, filed on 19 Mar 1998, PATENTED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ANITA L. MEIKLEJOHN, PH.D., FISH & RICHARDSON P.C., 225 Franklin Street, Boston, MA, 02110-2804
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 3790

AB Disclosed are methods for the treatment of proliferative disorders using compounds and/or environmental conditions which result in a difference in sensitivity of targeted and non-targeted cells. Certain of the methods involve the identification and use of allele-specific inhibitors of conditionally essential genes.

L49 ANSWER 39 OF 45 USPATFULL
ACCESSION NUMBER: 2002:198288 USPATFULL

TITLE: Modified adenovirus and uses thereof
INVENTOR(S): Young, Charles S.H., New York, NY, UNITED STATES
Hoey, Peter J., Belle Harbor, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002106382	A1	20020808
APPLICATION INFO.:	US 2001-904669	A1	20010713 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-218496P	20000714 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Cooper & Dunham LLP, 1185 Avenue of the Americas, New York, NY, 10036
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 1808
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a modified adenovirus comprising genomic adenoviral DNA which has been modified so that (i) the only gene product of the early region (E4) that is expressed is open reading frame 6 (ORF-6), (ii) neither the gene product of the E1A region nor the gene product of the E1B region is expressed, and (iii) no other early or late gene products are expressed. The present invention also provides methods of inhibiting repair of breaks in double-stranded DNA in a cell, preventing concatamerization of linear wild-type adenoviral DNA, inhibiting V(D)J recombination of nucleic acid sequences encoding immunoglobulins, preventing apoptosis, and preventing and treating cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L49 ANSWER 40 OF 45 USPATFULL
ACCESSION NUMBER: 2002:16850 USPATFULL
TITLE: Human stress array
INVENTOR(S): Chenchik, Alex, Palo Alto, CA, UNITED STATES
Lukashev, Matvey E., Newton, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002009730	A1	20020124
APPLICATION INFO.:	US 2001-782909	A1	20010213 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-441920, filed on 17 Nov 1999, UNKNOWN
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Bret E. Field, BOZICEVIC, FIELD & FRANCIS LLP, 200 Middlefield Road, Suite 200, Menlo Park, CA, 94025
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
LINE COUNT: 2377
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Human stress arrays and methods for their use are provided. The subject arrays include a plurality of polynucleotide spots, each of which is made up of a polynucleotide probe composition of unique polynucleotides corresponding to a human stress gene. The subject arrays find use in hybridization assays, particularly in assays for the identification of differential gene expression of human stress genes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L49 ANSWER 41 OF 45 USPATFULL

ACCESSION NUMBER: 2001:36603 USPATFULL
TITLE: Inhibitors of alternative alleles of genes encoding products that mediate cell response to environmental changes
INVENTOR(S): Housman, David E., Newton, MA, United States
Ledley, Fred D., Needham, MA, United States
Stanton, Jr., Vincent P., Belmont, MA, United States
PATENT ASSIGNEE(S): Variagenics, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6200754	B1	20010313	
APPLICATION INFO.:	US 1998-45054		19980319	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Schwartzman, Robert A.
ASSISTANT EXAMINER: Epps, Janet L.
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 3654
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are methods for the treatment of proliferative disorders using compounds and/or environmental conditions which result in a difference in sensitivity of targeted and non-targeted cells. Certain of the methods involve the identification and use of allele-specific inhibitors of conditionally essential genes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L49 ANSWER 42 OF 45 PCTFULL COPYRIGHT 2002 Univentio
ACCESSION NUMBER: 2001092562 PCTFULL ED 20020826
TITLE (ENGLISH): INHIBITING RETROTRANSPOSON AND RETROVIRAL INTEGRATION BY TARGETING THE ATM PATHWAY
TITLE (FRENCH): INHIBITION DE L'INTEGRATION DU RETROTRANSPOSON ET RETROVIRALE PAR CIBLAGE DE LA VOIE DE TRANSMISSION ATM
INVENTOR(S): O' CONNOR, Mark, James; JACKSON, Stephen, Philip; LAU, Alan
PATENT ASSIGNEE(S): KUDOS PHARMACEUTICALS LIMITED; O' CONNOR, Mark, James; JACKSON, Stephen, Philip; LAU, Alan
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2001092562	A2	20011206
DESIGNATED STATES	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 2001-GB2398	A	20010530
PRIORITY INFO.:	US 2000-60/208,672		20000530

ABEN Ataxia telangiectasia mutated (ATM)-dependent DNA damage signalling mechanisims are involved in retroviral and retrotransposon integration. Screening methods for inhibitors of retroviral and retrotranspons activity comprise inhibiting the ATM-dependent DNA damage signalling pathway, e.g. by disrupting interaction between components of the pathway. Inhibitors are useful as anti-retroviral agents, e.g. in inhibition of HIV.
ABFR Des mecanismes de signalisation des dommages a l'ADN dependants de l'ataxia telangiectasia mutee (ATM) sont impliques dans l'integration

retrovirale et du retrotransposon. Des methodes de ciblage des inhibiteurs de l'activite retrovirale et du retrotransposon consiste a inhiber la voie de transmission de signalisation des dommages a l'ADN dependants de l'ATM, par exemple par interruption de l'interaction entre des composes de la voie de transmission. On utilise les inhibiteurs comme des agents anti-retroviraux, par exemple dans l'inhibition du VIH.

L49 ANSWER 43 OF 45 PCTFULL COPYRIGHT 2002 Univentio
ACCESSION NUMBER: 2001090404 PCTFULL ED 20020826
TITLE (ENGLISH): DRUG SCREENING SYSTEMS AND ASSAYS
TITLE (FRENCH): SYSTEMES ET METHODES DE CRIBLAGE DE MEDICAMENTS
INVENTOR(S): WEST, Steve, Craig; HANAKAHI, Leslyn, Ann, Akemi; BARTLET-JONES, Michael
PATENT ASSIGNEE(S): IMPERIAL CANCER RESEARCH TECHNOLOGY LIMITED; WEST, Steve, Craig; HANAKAHI, Leslyn, Ann, Akemi; BARTLET-JONES, Michael
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2001090404	A1	20011129
DESIGNATED STATES	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 2001-GB2180	A	20010518
PRIORITY INFO.:	GB 2000-0012179.8		20000520
	US 2000-60/221,226		20000725
	US 2001-60/268,367		20010214

ABEN A method of stimulating non-homologous end-joining (NHEJ) of DNA the method comprising performing NHEJ of DNA in the presence of inositol hexakisphosphate (IP6) or other stimulatory inositol phosphate. An assay of a protein kinase wherein the assay comprises inositol hexakisphosphate (IP6) or other stimulatory inositol phosphate. The invention also provides screening assays for compounds which may modulate NHEJ and which may be therapeutically useful; and screening assays for compounds which may modulate **DNA-PK** and related protein kinases and which may be therapeutically useful. Methods of modulating NHEJ and protein kinases are also disclosed.

ABFR L'invention porte sur un procede de stimulation de mecanismes d'assemblage non homologue des terminaison d'ADN, ce procede consistant a realiser l'assemblage non homologue des terminaisons de l'ADN en presence d'hexakisphosphate inositol (IP6) ou autre phosphate inositol stimulateur. L'invention porte egalement sur le dosage d'une proteine kinase, ce dosage comprenant hexakisphosphate inositol (IP6) ou autre phosphate inositol stimulateur. L'invention porte encore sur des methodes de criblage de composes qui peuvent moduler l'assemblage non homologue des terminaisons et etre utiles d'un point de vue therapeutique, ainsi que sur des methodes de criblage de composes qui peuvent moduler ADN-PK et des proteines kinases apparentees et qui peuvent etre utiles d'un point de vue therapeutique. Des procedes de modulation des mecanismes d'assemblage non homologue des terminaisons, ainsi que des proteines kinases sont egalement decrits.

L49 ANSWER 44 OF 45 BIOTECHDS COPYRIGHT 2002 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 2002-06020 BIOTECHDS
TITLE: Stimulating non-homologous end-joining of DNA for treating cancer or retroviral infections, comprises performing end-joining of DNA in the presence of inositol hexakisphosphate or other stimulatory inositol phosphate;
vector-mediated DNA-dependent protein-kinase or DNA-ligase

gene transfer and expression in host cell for gene therapy

AUTHOR: WEST S C; HANAKAHI L A A; BARTLET-JONES M
PATENT ASSIGNEE: IMPERIAL CANCER RES TECHNOLOGY LTD
PATENT INFO: WO 2001090404 29 Nov 2001
APPLICATION INFO: WO 2000-GB2180 20 May 2000
PRIORITY INFO: US 2001-268367 14 Feb 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-075375 [10]
AN 2002-06020 BIOTECHDS

AB DERWENT ABSTRACT: NOVELTY - Stimulating (M) non-homologous end-joining (NHEJ) of DNA, comprises performing NHEJ of DNA in the presence of inositol hexakisphosphate (IP6) or another stimulatory inositol phosphate (SIP). DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an assay of NHEJ of DNA comprising IP6 or another SIP; (2) use of IP6 or other SIP for stimulating NHEJ of DNA; (3) a kit of parts comprising IP6 or other SIP and one or more of a DNA-dependent protein kinase (PK), **XRCC4**, **DNA ligase IV**, or a host cell expressing the protein and a suitable DNA substrate; (4) an assay of a PK or for NHEJ of DNA which comprises IP6 or other SIP; (5) a kit of parts comprising a PK, or a host cell expressing PK, and IP6 or other SIP; (6) identifying a compound which modulates or mimics the effect of IP6 or other SIP in stimulating NHEJ of DNA, by: (a) performing NHEJ of DNA in the presence of the IP6 or other SIP and determining the effect of a test compound on the NHEJ of DNA; or (b) determining in the presence of IP6 or other SIP, the effect of a test compound on the interactions between the components of NHEJ reaction mixture; (7) identifying a compound which modulates the NHEJ of DNA, by determining the effect of an inositol phosphate or its derivative on NHEJ of DNA; (8) identifying a compound which modulates or mimics the effect of IP6 or other SIP on PK, by determining in the presence of IP6 or other SIP, the effect of a test compound on the catalytic activity of PK or on the ability of PK to interact with another component; (9) identifying a compound which modulates the **binding** of IP6 or other SIP to a PK, **XRCC4** or **DNA ligase IV**, by determining whether a test compound reduces or increases the **binding** of IP6 or other SIP to PK or its subunit, **XRCC4** or **DNA ligase IV**; (10) a compound identifiable or identified by the above methods (6)-(8); (11) reducing NHEJ of DNA comprising reducing the amount of, or inhibiting the stimulatory effect of IP6 or other SIP in a NHEJ reaction; (12) enhancing NHEJ of DNA comprising increasing the amount of or enhancing or mimicking the stimulatory effect of IP6 or other SIP in an NHEJ reaction; (13) modulating the activity or interaction of PK by changing the amount of IP6 or other SIP present with PK, or inhibiting or enhancing the effect of IP6 or other SIP on PK; and (14) determining whether an individual has or is predisposed to a defect in DNA repair or cell cycle checkpoint control, by obtaining a sample from the patient, determining the concentration of, or subcellular localization of, IP6 or other SIP in the sample, and comparing the result with a standard. BIOTECHNOLOGY - Preferred Method: IP6 or other SIP is exogenous IP6 or other SIP. The NHEJ of DNA is performed in vitro in a NHEJ reaction mixture which includes DNA-dependent PK (or a component such as **Ku** 70/80 heterodimer or its subunit), **XRCC4**, **DNA ligase IV**, a suitable DNA substrate, ATP and Mg2+. PK has a domain with similarity to the catalytic domain of phosphatidylinositol 3-kinase and is chosen from: (i) DNA-dependent PK, ATR, ATM, FRAP; (ii) Saccharomyces cerevisiae gene products Tel1p, Mec1p, Tor1p or Tor2p; or (iii) Schizosaccharomyces pombe gene product Rad3. In method (8), the effect of a test compound on the interaction between the catalytic subunit of a DNA-dependent PK and any one of Ku70, Ku80, **DNA ligase IV**, **XRCC4** or its suitable DNA substrate is determined. In method (9), the subunit is the Ku70/80 heterodimer of **DNA-PK** or the Ku70 or Ku80 subunit. The test compound is an inositol derivative, a phosphoinositide

or an analog of IP6 or another SIP and a compound which mimics or modulates the effect of IP6 or other SIP is selected for further study. Preferred Kit: One or more of DNA dependent PK, **XRCC4** and **DNA ligase IV** are expressed from a recombinant nucleic acid molecule. PK is expressed from a recombinant nucleic acid and the kit further comprises a substrate for PK. ACTIVITY - Cytostatic; virucide; vasotropic; anti-HIV; immunomodulatory; MECHANISM OF ACTION - Gene therapy regimens improver; NHEJ of DNA modulator; protein kinase modulator. The stimulation of DNA-protein kinase (PK) dependent NHEJ by inositol phosphate was studied. Commercially available IP6 was assayed for its ability to stimulate end-joining by a cell extract which contained all components required for NHEJ in vivo (Ku70/80, DNA-PKcs, **XRCC4** and **DNA ligase IV**). IP6 stimulated end-joining at concentrations in the region of 100 nM and stimulation was maximal at 1 micro Molar. To assess the specificity of NHEJ for IP6, the ability of IP6 to stimulate end-joining with other inositol phosphates (IP5, IP4 and IP3) was compared. In addition, inositol hexasulfate (IS6), an inositol compound which provides a charge distribution similar to that of IP6, while presenting sulfate rather than phosphate groups was also assayed. It was found that IS6 was unable to stimulate end-joining, demonstrating a clear requirement for phosphate groups. IP6 proved to be the most effective inositol phosphate compound of those tested. IP5 and IP4 were also able to stimulate end-joining, but the efficiency of this stimulation was reduced relative to IP6. The data showed that end-joining required a phosphorylated inositol species, and the stimulation of NHEJ was directly related to the extend of phosphorylation. USE - (M) is useful for modulating NHEJ of DNA in a human or animal cell in need of reduction or enhancement in NHEJ of DNA and for treating cancer, augmenting cancer radiotherapy and/or chemotherapy regimes, improving gene therapy regimes, enhancing homologous recombination, treating retroviral infections, or modulating the immune system and to treat patients who are immunocompromized or susceptible to cancer due to impaired checkpoint cell cycle control. Compounds which may be useful in developing agents for treating the above conditions may be identified. Agents may be developed for modulating PK activity or interactions and for identifying compounds which modulate cell cycle checkpoint control (all claimed). Modulators of ATM or ATR are useful for treating ataxia-telangiectasia, acquired immunodeficiency syndrome (AIDS) and other conditions, modulating the immune system, telomere length and augmenting cancer and radiotherapy or chemotherapy. ADMINISTRATION - Administered by oral or parenteral, e.g. subcutaneous or intramuscular routes. No dosage is specified. (104 pages)

L49 ANSWER 45 OF 45 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-075375 [10] WPIDS
DOC. NO. CPI: C2002-022554
TITLE: Stimulating non-homologous end-joining of DNA for treating cancer or retroviral infections, comprises performing end-joining of DNA in the presence of inositol hexakisphosphate or other stimulatory inositol phosphate.
DERWENT CLASS: B04 D16
INVENTOR(S): BARTLET-JONES, M; HANAKAHI, L A A; WEST, S C
PATENT ASSIGNEE(S): (IMCR) IMPERIAL CANCER RES TECHNOLOGY LTD
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001090404	A1	20011129	(200210)*	EN	104

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001056530 A 20011203 (200221)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001090404 A1		WO 2001-GB2180	20010518
AU 2001056530 A		AU 2001-56530	20010518

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001056530 A	Based on	WO 200190404

PRIORITY APPLN. INFO: US 2001-268367P 20010214; GB 2000-12179 20000520; US 2000-221226P 20000725

AN 2002-075375 [10] WPIDS

AB WO 200190404 A UPAB: 20020213

NOVELTY - Stimulating (M) non-homologous end-joining (NHEJ) of DNA, comprises performing NHEJ of DNA in the presence of inositol hexakisphosphate (IP6) or another stimulatory inositol phosphate (SIP).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an assay of NHEJ of DNA comprising IP6 or another SIP;

(2) use of IP6 or other SIP for stimulating NHEJ of DNA;

(3) a kit of parts comprising IP6 or other SIP and one or more of a DNA-dependent protein kinase (PK), **XRCC4**, **DNA ligase IV**, or a host cell expressing the protein and a suitable DNA substrate;

(4) an assay of a PK or for NHEJ of DNA which comprises IP6 or other SIP;

(5) a kit of parts comprising a PK, or a host cell expressing PK, and IP6 or other SIP;

(6) identifying a compound which modulates or mimics the effect of IP6 or other SIP in stimulating NHEJ of DNA, by:

(a) performing NHEJ of DNA in the presence of the IP6 or other SIP and determining the effect of a test compound on the NHEJ of DNA; or

(b) determining in the presence of IP6 or other SIP, the effect of a test compound on the interactions between the components of NHEJ reaction mixture;

(7) identifying a compound which modulates the NHEJ of DNA, by determining the effect of an inositol phosphate or its derivative on NHEJ of DNA;

(8) identifying a compound which modulates or mimics the effect of IP6 or other SIP on PK, by determining in the presence of IP6 or other SIP, the effect of a test compound on the catalytic activity of PK or on the ability of PK to interact with another component;

(9) identifying a compound which modulates the **binding** of IP6 or other SIP to a PK, **XRCC4** or **DNA ligase IV**, by determining whether a test compound reduces or increases the **binding** of IP6 or other SIP to PK or its subunit, **XRCC4** or **DNA ligase IV**;

(10) a compound identifiable or identified by the above methods (6)-(8);

(11) reducing NHEJ of DNA comprising reducing the amount of, or inhibiting the stimulatory effect of IP6 or other SIP in a NHEJ reaction;

(12) enhancing NHEJ of DNA comprising increasing the amount of or enhancing or mimicking the stimulatory effect of IP6 or other SIP in an NHEJ reaction;

(13) modulating the activity or interaction of PK by changing the amount of IP6 or other SIP present with PK, or inhibiting or enhancing the effect of IP6 or other SIP on PK; and

(14) determining whether an individual has or is predisposed to a defect in DNA repair or cell cycle checkpoint control, by obtaining a

sample from the patient, determining the concentration of, or subcellular localization of, IP6 or other SIP in the sample, and comparing the result with a standard.

ACTIVITY - Cytostatic; virucide; vasotropic; anti-HIV; immunomodulatory;

MECHANISM OF ACTION - Gene therapy regimens improver; NHEJ of DNA modulator; protein kinase modulator. The stimulation of DNA-protein kinase (PK) dependent NHEJ by inositol phosphate was studied. Commercially available IP6 was assayed for its ability to stimulate end-joining by a cell extract which contained all components required for NHEJ in vivo (Ku70/80, DNA-PKcs, **XRCC4** and **DNA ligase IV**). IP6 stimulated end-joining at concentrations in the region of 100 nM and stimulation was maximal at 1 micro M. To assess the specificity of NHEJ for IP6, the ability of IP6 to stimulate end-joining with other inositol phosphates (IP5, IP4 and IP3) was compared. In addition, inositol hexasulfate (IS6), an inositol compound which provides a charge distribution similar to that of IP6, while presenting sulfate rather than phosphate groups was also assayed. It was found that IS6 was unable to stimulate end-joining, demonstrating a clear requirement for phosphate groups. IP6 proved to be the most effective inositol phosphate compound of those tested. IP5 and IP4 were also able to stimulate end-joining, but the efficiency of this stimulation was reduced relative to IP6. The data showed that end-joining required a phosphorylated inositol species, and the stimulation of NHEJ was directly related to the extend of phosphorylation.

USE - (M) is useful for modulating NHEJ of DNA in a human or animal cell in need of reduction or enhancement in NHEJ of DNA and for treating cancer, augmenting cancer radiotherapy and/or chemotherapy regimes, improving gene therapy regimes, enhancing homologous recombination, treating retroviral infections, or modulating the immune system and to treat patients who are immunocompromized or susceptible to cancer due to impaired checkpoint cell cycle control. Compounds which may be useful in developing agents for treating the above conditions may be identified. Agents may be developed for modulating PK activity or interactions and for identifying compounds which modulate cell cycle checkpoint control (all claimed). Modulators of ATM or ATR are useful for treating ataxia-telangiectasia, acquired immunodeficiency syndrome (AIDS) and other conditions, modulating the immune system, telomere length and augmenting cancer and radiotherapy or chemotherapy.

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